Immuno-Oncology
RESEARCH REVIEW™

Making Education Easy

Issue 1 – 2020

In this issue:

Abbreviations used in this issue

ALL/B-ALL = (B-cell) acute lymphoblastic leukaemia
BCMA = B-cell maturation antigen
BITE = bispecific T-cell engager
CAR = chimeric antigen receptor
COVID-19 = coronavirus disease 2019
CRS = cytokine-release syndrome
HR = hazard ratio
ICI = immune checkpoint inhibitor
MTD = maximum tolerated dose
OS = overall survival
PCTT = persistent cytopenias after T-cell therapy
PD-1 = programmed cell death-1
PFS = progression-free survival
SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2
SCT = stem-cell transplantation

Welcome to the first issue of Immuno-Oncology Research Review.

This review is a unique publication that aims to provide readers with topical and accessible information on the ever-developing and exciting field of immunotherapies for cancer. We do hope you enjoy this inaugural issue, for which we have included some of the pivotal research from the last few months, focusing on treatments that are relevant to the clinical setting. We would like to thank Dr Robert Weinkove for his contribution to this first edition. As with all Research Review publications, your comments and feedback are always welcome and can be submitted using my email address below or directly via the Research Review website.

Kind regards,

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KTE-X19 CAR T-cell therapy in relapsed or refractory mantle-cell lymphoma

Authors: Wang M et al.

Summary: In this phase 2 trial, patients with relapsed or refractory mantle-cell lymphoma following Bruton's tyrosine kinase inhibitor therapy underwent leukapheresis and optional bridging therapy, followed by conditioning chemotherapy and a single infusion of KTE-X19 CAR T-cells. The primary efficacy analysis was performed after 60 participants had been treated and followed for 7 months. For the primary efficacy analysis, the objective response rate was 93%, including a complete response rate of 67%. In an intent-to-treat analysis, the objective response rate was 85%, including a complete response rate of 59%. After median follow-up of 12.3 months, the remission rate in the primary efficacy analysis was 57%, and the respective 1-year PFS and OS rates were 61% and 83%. Grade ≥3 adverse events included cytopenias (94%), infections (32%, including two fatal), neurological events (31%) and CRS (15%).

Comment: Following very good response rates in diffuse large B-cell lymphoma, we are now seeing similar CAR T-cell therapy results in more indolent B-cell lymphomas. KTE-X19 is similar to Kite/Gilead's licensed CAR T-cell product, axicabtagene ciloleucel, but with manufacturing process changes. The impressive 12-month PFS (61%) and the apparent plateau of the PFS curve suggests CAR T-cells could compete with allogeneic SCT in this lymphoma. With no significant risk of graft-versus-host disease, and very low treatment-related mortality (3% in this trial), CAR T-cell therapies have some distinct advantages over allogeneic SCT. However, CAR T-cells are expensive, and have significant short-term toxicities: in this trial, grade 3 neurotoxicity was common, nearly all participants required tocilizumab, and cytopenias were common.

Reference: N Engl J Med 2020;382:1331–42
Abstract

Chimeric antigen receptor T cell therapy during the COVID-19 pandemic

Authors: Bachanova V et al., the CAR T-cell Consortium

Summary: Based on the collective experience of the CAR T-cell Consortium investigators, these authors reviewed and addressed several questions and concerns related to the use of cellular therapies in the setting of the COVID-19 pandemic. They provided general recommendations that address: i) necessary resources for safe cell therapy administration; ii) determinants of cell therapy utilisation; iii) patient selection for B-cell non-Hodgkin's lymphomas and B-ALL; iv) supportive measures during administration of cell therapies; v) use and prioritisation of tocilizumab; and vi) collaborative care with referring physicians. They also comment that these recommendations should be regarded as 'fluid', and that extensive consideration of the potential risks and benefits is needed before a decision to proceed with CAR T-cell therapy is made.

Comment: Although the first wave of COVID-19 appears to have been controlled in NZ and Australia, a risk of re-emergence remains. From cell harvest to administration and aftercare, CAR T-cell therapies involve a complex international supply chain, susceptible to disruption. The risks of CRS or neurotoxicity after CAR T-cell therapy mandate intensive care unit bed availability, which has been constrained in localities with major COVID-19 outbreaks. Finally, recipients of CAR T-cells are immunosuppressed for months after administration, and are presumably at high risk of severe COVID-19. These risks have to be balanced against the risk of leaving the underlying disease untreated. The recommendations in this guidance mirror those for haematopoietic SCT, and are consistent with recent COVID-19 consensus guidance for Australasian cancer centres.

Reference: Biol Blood Marrow Transplant; Published online April 14, 2020
Abstract

COVID-19: the use of immunotherapy in metastatic lung cancer

Authors: Davis AP et al.

Summary: These authors outlined challenges within thoracic oncology, where novel anticancer therapies such as immunotherapy have resulted in improvements in quality of life and life expectancy for significant numbers of patients. Initial data from China suggesting that these patients are at increased risk for serious events from COVID-19 should be considered when making decisions regarding patient selection for therapy, duration of therapy and the decision to combine immunotherapy with cytotoxic chemotherapy. Although gains associated with the introduction of anti-PD-1 therapy remain relevant during the ongoing COVID-19 pandemic, a subset of patients may be placed at increased risk.

Comment: People with cancer are at elevated risk of severe COVID-19, and those with lung cancer may be at particularly high risk due to their underlying lung disease. Of particular concern, the cardinal features of COVID-19 (cough, fever, hypoxia) can be clinically and radiologically indistinguishable from those of ICI-induced pneumonitis. Various society guidelines recommend clinicians consider the possibility of immune-related adverse events among ICI recipients with COVID-19, and *vice versa*. A low threshold for considering steroids for ICI recipients with COVID-19 might be warranted. Due to disease- and treatment-related risks, it seems likely that people with cancer will be advised to adhere to social distancing guidelines, and to limit overseas travel, for longer than the general population.

Reference: Immunotherapy 2020;12:545–8
Abstract

Insights from immuno-oncology: the Society for Immunotherapy of Cancer Statement on access to IL-6-targeting therapies for COVID-19

Authors: Ascierto PA et al.

Summary: This article from the Society for Immunotherapy of Cancer proposes that efforts should be made to maximise the compassionate use availability of anti-IL-6 agents (e.g. tocilizumab and sarilumab) for critically ill hospitalised patients with SARS-CoV-2 infection. The authors also comment that efforts should be made so clinicians and clinical investigators can access investigational anti-IL-6 agents. Additionally, they recommend that pharma and biotech companies consider facilitation of drug availability, and call on all involved to swiftly and creatively remove accessibility barriers for agents like anti-IL-6 agents in these extraordinary times.

Comment: Parallels have also been drawn between the systemic inflammation of severe COVID-19 and the IL-6-driven CRS observed after CAR T-cell therapies and BITEs. Retrospective data suggest the anti-cytokine therapy tocilizumab might reduce risk of death in severe COVID-19, and randomised trials are ongoing. If these trials are positive, a concern for clinicians administering CAR T-cell therapies and BITEs is that a global spike in demand for anti-cytokine therapies for COVID-19 could affect the availability of these important agents for immuno-oncology recipients.

Reference: J Immunother Cancer 2020;8:e000878
Abstract

Incidence and risk factors associated with a syndrome of persistent cytopenias after CAR-T cell therapy (PCTT)

Authors: Nahas GR et al.

Summary: These authors reported a case series of bone marrow failure syndromes with or without co-existing clonal myelodysplastic syndrome among patients treated with anti-CD19 CAR T-cells for refractory aggressive B-cell lymphomas; bone marrow failure was defined as an absolute neutrophil count <500 cells/μL on day 42 after CAR T-cell infusion, or filgrastim support to reach that number. 'Persistent cytopenias after T-cell therapy', or PCTT, was the term used to describe this syndrome, for which the incidence after axicabtagene ciloleucel administration was 38%. Independent predictors of PCTT were platelet count <75,000 cells/μL at the time lymphodepleting chemotherapy was started and maximum severity CRS on day 0 or 1 after CAR T-cell infusion.

Comment: As anti-CD19 CAR T-cell therapies become a standard of care for relapsed and refractory B-cell lymphomas in some jurisdictions, a better understanding of their toxicities is emerging. CAR T-cell-treating clinicians are familiar with cytopenias after CAR T-cell therapy. The field of immuno-oncology is rich in acronyms, and this group proposes a new one to add to the list: PCTT. Most CAR T-cell recipients will have received many prior lines of chemotherapy, often including haematopoietic SCT. It remains unclear whether PCTT is primarily attributable to these prior therapies, or to the CAR T-cells and associated lymphodepleting chemotherapy. This may become clearer in future, as CAR T-cell therapies are being introduced earlier in the disease course, and administered to patients who are less heavily pretreated.

Reference: Leuk Lymphoma 2020;61:940–3
Abstract

Blinatumomab consolidation and maintenance therapy in adults with relapsed/refractory B-precursor acute lymphoblastic leukemia

Authors: Rambaldi A et al.

Summary: The efficacy and safety of participants from a phase 3 trial who received additional cycles of blinatumomab were reported; 267 patients with relapsed or refractory ALL had received 6-week cycles of induction blinatumomab as a continuous intravenous infusion for 4 weeks, with those achieving a bone marrow response (≤5% blasts) or complete remission eligible for additional cycles (consolidation n=86; maintenance n=36). Compared with participants who did not receive maintenance blinatumomab, those who did showed evidence of longer median OS (not reached vs. 15.5 months) and longer median relapse-free survival (14.5 vs. 9.8 months). The respective incidences of adverse events during induction, consolidation and maintenance blinatumomab were 97.2%, 86.1% and 72.2%. There were no new safety signals recorded.

Comment: BITEs, such as the licensed agent blinatumomab, are small molecules that directly bind malignant cells (via CD19 in this case) and T-cells, bringing the cells together, and activating the T-cells to kill the tumour cell. Blinatumomab is the first agent of this class, and has impressive response rates in B-ALL. Unlike CAR T-cell therapies, however, blinatumomab is very short-lived, and relapse typically occurs once treatment is stopped. This follow-up analysis of the blinatumomab registration trial shows that maintenance can be associated with durable responses in relapsed/refractory B-ALL. Very few participants either entered (n=36, 13%) or completed (n=11, 4%) maintenance therapy, presumably because those who could, proceeded to consolidation allogeneic SCT. Blinatumomab has unfavourable pharmacokinetics, requiring a 4-week continuous intravenous infusion – newer BITEs are overcoming this limitation.

Reference: Blood Adv 2020;4:1518–25
Abstract

Anti-B-cell maturation antigen BiTE molecule AMG 420 induces responses in multiple myeloma

Authors: Topp MS et al.

Summary: In this phase 1, first-in-human study, 42 patients with relapsed or refractory multiple myeloma received up to ten 6-week cycles of dose-escalated intravenous AMG 420 (an anti-BCMA BITE) 0.2–800 µg/day by 4-week continuous infusions; a median of one cycle was given with only three participants receiving the full 10 cycles. Discontinuations were due to disease progression (n=25), adverse events (n=7), death (n=4) and withdrawn consent (n=1). Two participants were still on treatment at the time of reporting. The serious adverse event rate was 48%, and the response rate was 31%. At the MTD (400 µg/day), the overall response rate was 70%, including five minimal residual disease-negative complete responses, one partial response and one very good partial response. All responses at the MTD were observed during cycle one, and responses lasted for a median of 9 months.

Comment: BCMA is highly expressed on plasma cells, and is proving a valuable target for myeloma immunotherapy, with high response rates for anti-BCMA CAR T-cells. This phase 1 trial of an anti-BCMA BITE resulted in high overall responses at the MTD, although the short half-life of this agent requires continuous infusion. CRS was mild, but as for CAR T-cell therapies, infections remain an issue, and a safety signal of transaminitis was observed (although most cases were mild and reversable). If pharmacokinetic and any toxicity issues can be overcome, anti-BCMA BITEs could present a useful treatment modality for myeloma.

Reference: J Clin Oncol 2020;38:775–83
Abstract

Association between immune-related adverse events and recurrence-free survival among patients with stage III melanoma randomized to receive pembrolizumab or placebo

Authors: Eggermont AMM et al.

Summary: This was a secondary analysis of a trial that randomised adults with stage 3 melanoma to receive pembrolizumab 200mg (n=509) or placebo (n=502) every 3 weeks for a total of 18 doses or until disease recurrence, unacceptable toxic effects, major protocol violation or consent withdrawal. Compared with placebo, pembrolizumab recipients had longer relapse-free survival among treatment initiators (HR 0.56 [98.4% CI 0.43, 0.74]), but a higher incidence of immune-related adverse events (37.4% vs. 9.0%). The occurrence of an immune-related adverse event was associated with longer relapse-free survival among pembrolizumab recipients (HR 0.61 [95% CI 0.39, 0.95]); this association was not significant in the placebo arm. Compared with placebo, pembrolizumab was associated with a greater reduction in the hazard of recurrence or death after the onset of an immune-related adverse event than without or before an immune-related adverse event (HR 0.37 vs. 0.61 [p=0.03]).

Comment: Clinicians prescribing ICIs will be familiar with immune-related adverse events. As well as enhancing T-cell responses against the tumour, ICIs can 'unleash' T-cells with autoimmune potential. This secondary analysis of the KEYNOTE-054 trial found that immune-related adverse events were associated with improved relapse-free survival in the pembrolizumab arm, but not the placebo arm. Most immune-related adverse events were endocrine or cutaneous. Patients who developed vitiligo appeared to be at particularly low risk of melanoma recurrence, presumably reflecting the benefit of unleashing T-cell responses directed against antigens shared by normal and malignant melanocytes. The use of systemic steroids to treat an immune-related adverse event was associated with a diminished (but not absent) pembrolizumab treatment effect.

Reference: JAMA Oncol 2020;6:519–27
Abstract

Are immune-related adverse events associated with the efficacy of immune checkpoint inhibitors in patients with cancer?

Authors: Zhou X et al.

Summary: This was a systematic review with meta-analysis of 30 studies (n=4971) reporting on efficacy and immune-related adverse events associated with ICIs in patients with cancer. Compared with patients who did not develop an immune-related adverse event, those who did had superior OS and PFS (respective HRs 0.54 [95% CI 0.45, 0.65] and 0.52 [0.44, 0.61]); these findings persisted in subgroup analyses by study quality characteristics and cancer types, and in specific analyses of endocrine, dermatological and low-grade immune-related adverse events (0.52 [0.44, 0.62], 0.45 [0.35, 0.59] and 0.57 [0.43, 0.75] for OS). The association between immune-related adverse events and OS benefit was significant for patients treated with PD-1 inhibitors (HR 0.51 [95% CI 0.42, 0.62]) or ICI monotherapy (0.53 [0.43, 0.65]), but not for those who received cytotoxic T-cell antigen-4 inhibitors (0.89 [0.49, 1.61]) or ICIs in combination with other therapies (0.62 [0.36, 1.05]).

Comment: This systematic review and meta-analysis found an association between immune-related adverse events and improved OS and PFS following treatment with PD-1 inhibitors, across multiple malignancies. The association was most convincing for grade 1–2 endocrine and skin immune-related adverse events, while (in part due to smaller numbers) an adverse effect of severe, pulmonary or hepatobiliary immune-related adverse events on survival was not excluded. Overall, this analysis supports the notion that immune-related adverse events are an indicator of ICI efficacy, and that mild endocrine and skin immune-related adverse events should not dissuade long-term resumption of anti-PD-1 therapy. In contrast, severe, pulmonary or hepatobiliary immune-related adverse events are likely to require treatment discontinuation.

Reference: BMC Med 2020;18:87
Abstract

Value and affordability of CAR T-cell therapy in the United States

Authors: Fiorenza S et al.

Summary: This review summarised recent, peer-reviewed cost-effectiveness studies of tisagenlecleucel and axicabtagene ciloleucel in the US. Key issues concerning the health plan budget impact of CAR T-cell therapy were discussed, as were review policy, payment and scientific approaches that may improve CAR T-cell therapy value and affordability.

Comment: Financial toxicity is an issue for most new cancer therapies, and as personalised cell therapies, commercial CAR T-cells are no exception. As well as high manufacturing, testing and shipping costs, the costs of administration, toxicity management and follow-up need to be taken into consideration. This review, by authors including expat Kiwi haematologist David Ritchie, notes that cost per quality-adjusted life-year is most acceptable for children and young adults, and for CAR T-cell therapies with a high probability of 'cure'. In future, cost effectiveness should improve through manufacturing advances (including automation, local manufacture and cheaper gene transfer systems), competition and products with higher response rates and/or lower toxicity rates. In the short term, the prospects for funded CAR T-cell therapy in NZ may be best for the small number of children and young adults with refractory B-ALL, while clinical trial access may remain the only avenue for adults unable to self-fund.

Reference: Bone Marrow Transplant; Published online May 30, 2020
Abstract

Independent commentary by Dr Robert Weinkove

Dr Robert Weinkove is a Consultant Haematologist at Wellington Blood & Cancer Centre and Clinical Director at the Malaghan Institute of Medical Research. His clinical and research interests include B-cell malignancies and cancer immunotherapy. He provides clinical oversight for the cell therapy facility at the Malaghan Institute and is Principal Investigator of New Zealand's first CAR T-cell trial, 'ENABLE' (NCT04049513). He studied medicine at the University of Cambridge and Kings College London, trained in General Medicine and Haematology at Guy's and St Thomas' Hospitals in London and the Medizinische Hochschule Hannover in Germany, and completed an Immunology PhD with the University of Otago.